

FORM PTO-1390  
(REV. 5-93)U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTORNEY'S DOCKET NUMBER  
2565/86**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

**09/868950**INTERNATIONAL APPLICATION NO.  
PCT/EP99/10338INTERNATIONAL FILING DATE  
(23.12.99)  
23 December 1999PRIORITY DATES CLAIMED  
(24.12.98)  
24 December 1998TITLE OF INVENTION  
METHOD FOR DETERMINING THE DISTRIBUTION VOLUME OF A BLOOD COMPONENT DURING AN  
EXTRACORPOREAL BLOOD TREATMENT AND APPARATUS FOR IMPLEMENTING THE METHODAPPLICANT(S) FOR DO/EO/US  
GOLDAU, Rainer; GRAF, Thomas and GROSS, Malte.

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
  2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
  3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) immediately rather than delay applicable time limit set in 35 U.S.C. examination until the expiration of the 371(b) and PCT Articles 22 and 39(1).
  4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
  5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
    - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b. ☒ has been transmitted by the International Bureau.
    - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
  6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
    - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
    - b. ☐ have been transmitted by the International Bureau.
    - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
    - d. ☒ have not been made and will not be made.
  8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
  10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11. to 16. below concern other document(s) or information included:**
11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
  12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
  13. ☐ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
  14. ☐ A substitute specification and marked-up specification.
  15. ☐ A change of power of attorney and/or address letter.
  16. ☐ Other items or information:

Express Mail No.: EL244505895US

U.S. APPLICATION NO. **09/868950**INTERNATIONAL APPLICATION NO.  
PCT/EP99/10338ATTORNEY'S DOCKET NUMBER  
2565/8617. ☒ The following fees are submitted:**Basic National Fee (37 CFR 1.492(a)(1)-(5)):**

Search Report has been prepared by the EPO or JPO ..... \$860.00  
 International preliminary examination fee paid to USPTO (37 CFR 1.482) ... \$690.00  
 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but  
 international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$710.00  
 Neither international preliminary examination fee (37 CFR 1.482) nor international  
 search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$1,000.00  
 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all  
 claims satisfied provisions of PCT Article 33(2)-(4) ..... \$100.00

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**ENTER APPROPRIATE BASIC FEE AMOUNT =**

\$ 860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months  
 from the earliest claimed priority date (37 CFR 1.492(e)).

\$

Claims

Number Filed

Number Extra

Rate

Total Claims

25 - 20 =

5

X \$18.00

\$ 90.00

Independent Claims

4 - 3 =

1

X \$80.00

\$ 80.00

Multiple dependent claim(s) (if applicable)

+ \$270.00

\$ 270.00

**TOTAL OF ABOVE CALCULATIONS =**

\$1,300.00

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 also be filed. (Note 37 CFR 1.9, 1.27, 1.28).

\$

**SUBTOTAL =**

\$1,300.00

Processing fee of \$130.00 for furnishing the English translation later the ☐ 20 ☐ 30  
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+

\$

**TOTAL NATIONAL FEE =**

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Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be  
 accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property

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**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a)  
 Deposit Account No. or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

David Greenbaum, Reg. No. 46,739  
 NAME

DATE

6/22/01



26646

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DATE OF DEPOSIT 6/22/01

TYPE OF DOCUMENT National Phase Patent Application  
Re: Goldan et al

SERIAL NO. To be Assigned FILING DATE Herewith

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE, BY BEING HANDED TO A POSTAL CLERK OR BY BEING PLACED IN THE EXPRESS MAIL BOX BEFORE THE POSTED DATE OF THE LAST PICK UP, AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.

Miran Soroka  
(PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Miran Soroka  
(SIGNATURE OF PERSON MAILING PAPER OR FEE)  
Method for determining the distribution  
volume of a blood component during  
an extracorporeal blood treatment  
and apparatus for implementing the  
method

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09/868950  
JC18 Rec'd PCT/PTO 22 JUN 2001

[2565/86]

METHOD FOR DETERMINING THE DISTRIBUTION VOLUME OF A  
BLOOD COMPONENT DURING AN EXTRACORPOREAL BLOOD TREATMENT  
AND APPARATUS FOR IMPLEMENTING THE METHOD

5 The present invention relates to a method for determining  
the distribution volume of a blood component in the body  
of an organism, particularly the urea distribution  
volume, during an extracorporeal blood treatment. In  
addition, the present invention relates to an apparatus  
for determining the distribution volume of a blood  
component in the body of an organism during an  
extracorporeal blood treatment in conjunction with a  
device for the extracorporeal blood treatment.

10 An essential task of the human kidneys is the separation  
of substances, usually eliminated with urine, from the  
blood, and the regulation of the water and electrolyte  
excretion. Hemodialysis represents a treatment method to  
15 compensate for dysfunctions of the kidneys with respect  
to the removal of substances usually eliminated with  
urine, and the adjustment of the electrolyte  
concentration in the blood.

20 During hemodialysis, the blood is conducted in an  
extracorporeal circuit through the blood chamber of a  
dialyzer, the blood chamber being separated from a  
dialyzing-fluid chamber by a semipermeable membrane. A  
dialyzing fluid containing the blood electrolytes in a  
25 specific concentration flows through the dialyzing-fluid  
chamber. The substance concentration (cd) of the  
dialyzing fluid corresponds to the concentration of the  
blood of a healthy individual. During the treatment, the  
blood of the patient and the dialyzing fluid are

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conducted past both sides of the membrane, generally in counterflow with a predefined flow rate ( $Q_b$  and  $Q_d$ , respectively). The substances usually eliminated with urine diffuse through the membrane from the blood chamber into the chamber for dialyzing fluid, while at the same time, electrolytes present in the blood and in the dialyzing fluid diffuse from the chamber of higher concentration to the chamber of lower concentration. The substance exchange can be additionally influenced by applying a trans-membrane pressure.

To permit optimization of the blood-treatment process, the determination of parameters for the hemodialysis during the extracorporeal blood treatment (in-vivo) is necessary. Of interest is the value for the exchange efficiency of the dialyzer, which is represented by the so-called "clearance" or "dialysance D".

Designated as clearance for a specific substance K is that virtual (calculated) blood volume which is completely freed of a specific substance per minute under defined conditions in the dialyzer. The dialysance D is a further concept for determining the performance of a dialyzer, in which the concentration of the eliminated substance in the dialyzing fluid is taken into account. In addition to these parameters for describing the performance of the dialyzer, other parameters are also important, such as the values for the aqueous component of the blood, the blood volume and the blood input concentration, etc.

The mathematical quantification, using measuring techniques, of the blood-purification process and the determination of the aforesaid parameters of the dialysis are relatively complex. With respect to the computational

fundamentals, reference is made to J. A. Sargent, F. A. Gotch: "Principles and Biophysics of Dialysis" in: *Replacement of Renal Function by Dialysis*, C. Jacobs, C. M. Kjellstrand, K. M. Koch, J. F. Winchester (editor), Kluwer Academie Publisher, Dordrecht, 1996.

The dialysance, i.e. the clearance can be determined as follows for a given electrolyte, e.g. sodium, at an ultra-filtration rate of zero. The dialysance D is equal to the relationship between the mass transport on the blood side for this electrolyte ( $Q_b \times (c_{bi} - c_{bo})$ ) and the concentration difference of this electrolyte between the blood and the dialyzing fluid at the respective input of the dialyzer ( $c_{bi} - c_{di}$ ).

$$D = Q_b \cdot \frac{c_{bi} - c_{bo}}{c_{bi} - c_{di}} \quad (1)$$

For reasons of mass balance, the following is applicable:

$$Q_b \cdot (c_{bi} - c_{bo}) = -Q_d \cdot (c_{di} - c_{do}) \quad (2)$$

Following from the two equations (1) and (2) indicated above is:

$$D = -Q_d \cdot \frac{c_{di} - c_{do}}{c_{bi} - c_{di}} \quad (3)$$

In this context, in (1) through (3):

$Q_b$  = effective flow of blood

$Q_d$  = flow of dialyzing fluid

$c_b$  = substance concentration in the blood

$c_d$  = substance concentration in the dialyzing fluid

$i$  = input of the dialyzer

o = output of the dialyzer

The effective blood flow is the flow of the blood component in which the substances to be removed are dissolved, i.e. it relates to the (aqueous) solution volume for this substance. Depending on the substance, it can be the plasma water flow or the blood serum flow, i.e. the entire water content in the whole blood. If the whole-blood flow  $Q_{vb}$  is ascertained, then  $Q_b$  can be determined from  $Q_{vb}$  using a constant factor.

In the event that the ultrafiltration rate  $Q_f$  is not equal to zero, dialysance  $D$  is calculated as follows:

$$D = \left[ Q_d \frac{c_{do} - c_{di}}{c_{bi} - c_{di}} \right] \cdot \left[ 1 - \frac{Q_f}{Q_b} \right] + Q_f \quad (4a)$$

The diffusive component of the dialysance  $D_{diff}$  is then calculated as follows:

$$D_{diff} = \left[ Q_d \frac{c_{do} - c_{di}}{c_{bi} - c_{di}} \right] \cdot \left[ 1 - \frac{Q_f}{Q_b} \right] \quad (4b)$$

For ionic substances, the Gibb's Donnan coefficient must be taken into account for the blood input concentration. For this, reference is made to the article by Sargent and Gotch cited above. For the sake of simplicity, this correction factor is omitted in the following.

The German patent DE 39 38 662 C2 (EP 0 428 927 A1) describes a method for the in-vivo determination of parameters for the hemodialysis, in which the





which parameters are entered such as the body size and the weight of the patient to be treated. The value ascertained for V is admittedly very imprecise.

5 A method is known from WO 98/55166 for determining the mass of a constituent such as urea in the blood, in which the concentration of the constituent in the dialyzing fluid is measured downstream of the dialyzer during the treatment. The mass of the constituent is determined from  
10 the change in the concentration as a function of time. The distribution volume should be calculated from the mass of the constituent. It is disadvantageous that the distribution volume is not determined continually, but rather only at the end of a treatment segment.

15 The object of the present invention is to specify a method which allows rapid and automated determination of the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment. A further objective underlying the present invention is  
20 to provide an apparatus for determining the distribution volume of a blood component in the body of an organism.

25 This objective is achieved according to the present invention by the features specified in Patent Claims 1 and 10, respectively.

30 Determination of the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment is based on the change in a physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path during the blood treatment and the measurement of the physical or chemical characteristic of the dialyzing fluid downstream of the

dialyzer. The physical or chemical characteristic of the dialyzing fluid is altered in the dialyzing-fluid path upstream from the dialyzer. In this context, the physical or chemical characteristic should be adjusted to physiologically tenable values.

If the change in the characteristic upstream of the dialyzer is known, it is possible to dispense with this measurement. Otherwise the characteristic is measured not only downstream, but also upstream of the dialyzer.

The change in the concentration of the blood component in the blood as a function of time is determined from the physical or chemical characteristic of the dialyzing fluid downstream of the dialyzer. The distribution volume of the substance in the body of an organism is then inferred from the change in the concentration of the blood component in the blood over time.

The physical or chemical characteristic of the dialyzing fluid upstream and downstream of the dialyzer is advantageously the concentration of a substance in the dialyzing fluid upstream and downstream of the dialyzer (dialyzing fluid input concentration and output concentration  $c_{di}$ ,  $c_{do}$ ). A deviation in the dialyzing fluid input concentration from the blood input concentration  $c_{bi}$  leads to a change in the blood input concentration  $c_{bi}$  at the dialyzer, since the measured substance shifts to or from the blood side. The distribution volume of this substance in the blood is then inferred from the change in the blood input concentration as a function of time.

To determine the distribution volume of sodium in the blood, preferably the conductivity of the dialyzing fluid is measured as a physical or chemical characteristic. The known conductivity sensors can be used for this purpose.

The urea distribution volume can be inferred from the sodium distribution volume, since the urea distribution volume corresponds essentially to the sodium distribution volume.

After the urea distribution volume is determined, the so-called "Kt/V" parameter can be calculated, in doing which the clearance K can either be ascertained according to the method known from DE 39 38 662 C2, or gathered from corresponding tables for the individual types of dialyzer.

In calculating the distribution volume V, the starting point is initially the following mass balance equation:

$$\int_t^{t+\Delta t} Q_d * c_{di}(t') dt' - \int_t^{t+\Delta t} (Q_d + Q_f) * c_{do}(t') dt' = V(t + \Delta t) * c_{bi}(t + \Delta t) - V(t) * c_{bi}(t) \quad (5)$$

Equation (5) represents how the blood concentration  $c_{bi}$  changes on the basis of the shift of substances into or out of the blood. If equation (5) is divided by  $\Delta t$  and the limiting value  $\Delta t \rightarrow \infty$  is then considered, then the integral mass balance according to equation (5) is converted into a differential mass balance:

$$Q_d * c_{di}(t) - (Q_d + Q_f) * c_{do}(t) = c_{bi}(t) \frac{dV(t)}{dt} - V(t) \frac{dc_{bi}(t)}{dt} \quad (6)$$

Solved according to  $dcbi(t)/dt$  and with  $dV(t)/dt = -Qf$ ,  
this yields equation (7):

$$\frac{dcbi}{dt} = \frac{Qd * cdi(t) - (Qd + Qf) * cdo(t) + Qf * cbi(t)}{V(t)} \quad (7)$$

Equation (7) represents the basis for the continuing  
considerations, it being assumed that the time profile of  
 $cdi(t)$  leads to a change of  $cbi(t)$ , and the measuring  
time is conditional upon a sufficient mixture in the  
blood of the patient.

Equation (7) can be evaluated in widely varying forms. If  
one assumes  $cdi(t) = \text{const}$ , as well as  $cdo(t) \approx \text{const}$  and  
 $cbi(t) \approx \text{const}$  during the measuring phase, which is well  
fulfilled for the case of a concentration gradient,  
changing only insignificantly during the measuring time,  
between the two fluids (i.e. the numerator in (7) changes  
only insignificantly), then applicable for the period of  
time  $t$  to  $t + \Delta t$  is:

$$V(t) = \frac{(Qd * cdi(t) - (Qd + Qf) * cdo(t) + Qf * cbi(t)) \Delta t}{cbi(t + \Delta t) - cbi(t)} \quad (8)$$

The physical or chemical characteristic of the dialyzing  
fluid upstream of the dialyzer is preferably increased  
abruptly from an original value to a predefined value, to  
then be abruptly reduced to a predefined value, whereupon  
the original value is set again. If the value by which  
the characteristic is reduced is twice as large as the  
value by which the characteristic is increased, and the  
time interval in which the characteristic is increased is

equal to the time interval in which the characteristic is reduced, then a symmetrical time profile is present which simplifies the evaluation, since the increase in the characteristic is offset by its decrease. In order not to have to feed to or remove from the patient unnecessary amounts of, for example, sodium during the treatment, the initial value of the characteristic in the dialyzing fluid, which is altered during the measurement, should correspond to the value in the blood.

In the event of unsymmetrical pulses for the two rectangular profiles, the change of the concentration in the blood as a function of time can be exactly calculated by forming a relationship between integral surfaces.

Determining the distribution volume is advantageously even further simplified because during the measurement, the volume of the dialyzing fluid flowing into the dialyzer is equal to the volume of fluid flowing out of the dialyzer. This can be accomplished using the familiar balancing devices. However, it is also possible to ascertain the distribution volume during a continuing ultrafiltration of the blood.

The distribution volume of a blood component in the body of an organism can then also be determined without explicitly ascertaining the change in the concentration of the component in the blood as a function of time.

An exemplary embodiment of a hemodialysis device having an apparatus for determining the urea distribution volume is further described in the following with reference to the drawing, in which:

Figure 1 shows a simplified schematic representation of a hemodialysis device having the apparatus for determining the urea distribution volume; and

Figure 2 shows the time profile of the dialyzing-fluid input and output concentration.

The apparatus for determining the urea distribution volume can form a separate subassembly. However, it can also be a component of a hemodialysis device, particularly since some components of the apparatus for determining the urea distribution volume are already present in the known dialyzers. In the following, the apparatus for determining the urea distribution volume is described together with the essential components of the dialyzer.

The hemodialysis device has a dialyzer 1 which is separated by a semi-permeable membrane 2 into a blood chamber 3 and a dialyzing-fluid chamber 4. The inlet of the blood chamber is connected to one end of a blood feed line 5 into which a blood pump 6 is switched, while the outlet of blood chamber 3 is connected to the one end of a blood discharge line 7 into which a drip chamber 8 is switched.

The dialyzing-fluid system of the hemodialysis device includes a device 9 for preparing the dialyzing fluid, with which different compositions of the dialyzing fluid (electrolyte dose) can be preselected. Preparation device 9 has a device 17 for altering the substance concentration of the dialyzing fluid, preferably the sodium concentration. A balancing device is also provided which includes two parallel-connected balance chambers

that are each subdivided into two balance-chamber halves. For the sake of greater clarity, only the two balance-chamber halves of one balance chamber are shown here. Preparation device 9 is connected to the inlet of first chamber half 11a of balancing device 11 via first section 10a of a dialyzing-fluid feed line 10. Second section 10b of dialyzing-fluid feed line 10 connects the outlet of first balancing-chamber half 11a to the inlet of dialyzing-fluid chamber 4. The outlet of dialyzing-fluid chamber 4 is connected via first section 12a of a dialyzing-fluid discharge line 12 to the inlet of second balancing-chamber half 11b. A dialyzing-fluid pump 13 is switched into first section 12a of dialyzing-fluid discharge line 12. The outlet of second balancing-chamber half 11b is connected to a drain 14 via second section 12b of dialyzing-fluid discharge line 12. Upstream of dialyzing-fluid pump 13, an ultrafiltrate line 15 branches off from dialyzing-fluid discharge line 12 and likewise leads to drain 14. An ultrafiltration pump 16 is switched into ultrafiltrate line 15.

The hemodialysis device also includes a central control unit 18 that is connected via control lines 19 through 22 to blood pump 6, dialyzing-fluid pump 13, ultrafiltration pump 16 and device 17 for altering the sodium concentration of the dialyzing fluid.

During the dialysis treatment, the blood of the patient flows through blood chamber 3, and the dialyzing fluid flows through dialyzing-fluid chamber 4 of dialyzer 1. Since balancing device 11 is switched into the dialyzing-fluid path, only so much dialyzing fluid can flow in via dialyzing-fluid feed line 10 as can flow off via dialyzing-fluid discharge line 12. Fluid can be

withdrawn from the patient using ultrafiltration pump 16, the desired ultrafiltration rate being predetermined by the control unit.

5 Measuring devices 23, 24, respectively, are arranged in feed line 10 and discharge line 12 upstream and downstream of dialyzer 1 for determining the substance concentration of the dialyzing fluid at the input of dialyzer 1 (dialyzing-fluid input concentration cdi) and  
10 the substance concentration of the dialyzing fluid at the output of the dialyzer (dialyzing-fluid output concentration cdo). Measuring devices 23, 24 for determining the dialyzing-fluid input and output concentration have conductivity sensors which preferably  
15 measure the temperature-corrected conductivity of the dialyzing fluid and thus especially the Na concentration. Instead of conductivity sensors, optical or other sensors, e.g. enzyme sensors, can also be arranged in the dialyzing-fluid path for measuring the dialyzing-fluid  
20 input and output concentration.

Arithmetic and evaluation unit 29 is connected via a data line 32 to control unit 18 in order to be able to retrieve flow rates Qb, Qd for blood and dialyzing-fluid  
25 pumps 6, 13.

Measuring devices 23, 24 are connected via data lines 25, 26 to a memory unit 27. Memory unit 27 receives the measured values of sensors and stores them in  
30 chronological sequence. The measured values are supplied via a data line 28 to an arithmetic and evaluation unit 29 which, in a digital computer (microprocessor), determines the urea distribution volume from the data obtained. The urea distribution volume is displayed on a



readout mechanism 30 that is connected via a data line 31 to arithmetic and evaluation unit 29.

The apparatus operates as follows for determining the urea distribution volume:

At the beginning of the measurement, control unit 18 halts ultrafiltration pump 16, so that the ultrafiltration rate is equal to 0. The control unit predefines flow rates  $Q_b$  and  $Q_d$  for the flow of the blood and dialyzing fluid.

The dialyzing fluid flows through the dialyzing-fluid chamber with a flow rate  $Q_d$  predefined by the speed of pump 13, and with dialyzing-fluid input concentration  $c_{di}$  which is set by device 17 and which is detected by measuring device 23 arranged upstream of the dialyzer. The dialyzing-fluid output concentration  $c_{do}$  appearing in response to the dialysis is detected by measuring device 24 arranged downstream of the dialyzer.

Device 17 adjusts a dialyzing-fluid input concentration  $c_{di}(t)$  which has the time profile shown in Figure 2. Starting from a value  $c_{di_0}$  which is customary for the dialysis treatment and which corresponds or at least comes close to the value  $c_{bi_0}$  of the sodium concentration in the blood upstream of the dialyzer, the input concentration is increased to the value  $c_{di_1}$  at point of time  $t_0$ . At point of time  $t_1$ , the input concentration is reduced to the value  $c_{di_2}$ , to then be set again to the original value  $c_{di_0}$  at point of time  $t_2$ .

Figure 2 shows, in dotted lines, the time profile of dialyzing-fluid output concentration  $c_{do}(t)$  appearing

downstream of the dialyzer.  $cdi_0 = cdo_0$  is for  $t < t_0$ . At the end of time interval  $t_0 < t < t_1$ , a value  $cdo_1$  appears at the dialyzer output, while at the end of time interval  $t_1 < t < t_2$ , a value  $cd_{02}$  appears at the dialyzer output. For  $t > t_2$ , the dialyzing-fluid output concentration again assumes the value of the dialyzing-fluid input concentration with sufficient accuracy.

The dialyzing-fluid input and output concentrations exhibit a symmetrical time profile. The value by which the input concentration is reduced is twice as large as the value by which the input concentration is increased. Time interval  $t_1 - t_0$  is equal to time interval  $t_2 - t_1$ . The time intervals are regulated such that in each case stable values ensue for  $cdo$ . Since the profile is symmetrical, the shift of electrolytes via the membrane of the dialyzer, caused by the first change, is compensated for again.

While the dialyzing-fluid input concentration is changed, the dialyzing-fluid input and output concentrations  $cdi_0$ ,  $cdo_0$  within time interval  $t < t_0$ ,  $cdi_1$ ,  $cdo_1$  within time interval  $t_0 < t < t_1$  and  $cdi_2$ ,  $cdo_2$  within time interval  $t_1 < t < t_2$  are measured and stored in memory unit 27. In so doing, it is taken into account that the values for  $cdo$  are time-displaced by a delay time  $t_d$  with respect to those of  $cdi$ .

Since the shift of electrolytes via the dialysis membrane, caused by the first change, is compensated for again in the symmetrical case, the following applies:

$$cdi_0 = cbi_0 = cbi_2 \quad (9)$$

points of time immediately prior to the change of cdi being designated in each case with the subscript as  $t_0$ ,  $t_1$  and  $t_2$ .

5 The change as a function of time in the blood-input concentration  $\Delta cbi$  is calculated as follows:

$$\Delta cbi = cbi_1 - cbi_0 \quad (10)$$

10

On condition that an ultra-filtration rate of zero ( $Q_f=0$ ) is set, and assuming that dialysance D does not change during the measurement, arithmetic and evaluation unit 29 calculates  $\Delta cbi$  from the stored values  $cdi_0$ ,  $cdo_0$ ,  $cdi_1$ ,  $cdo_1$  and  $cdi_2$ ,  $cdo_2$ , as well as from the adjusted dialyzing-fluid flow rate  $Q_d$  on the basis of the following equations:

15

20

$$D = \frac{[(cdo_0 - cdi_0) - (cdo_1 - cdi_1)]Q_d}{(cbi_0 - cdi_0) - (cbi_1 - cdi_1)} \quad (11)$$

25

$$D = \frac{[(cdo_1 - cdi_1) - (cdo_2 - cdi_2)]Q_d}{(cbi_1 - cdi_1) - (cbi_2 - cdi_2)} \quad (12)$$

30

$$D = \frac{[(cdo_0 - cdi_0) - (cdo_2 - cdi_2)]Q_d}{(cbi_0 - cdi_0) - (cbi_2 - cdi_2)} \quad (13)$$

35 In these three equations, only D and  $\Delta cbi$  are unknown.

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The arithmetic unit ascertains these parameters either from two equations hereof, from average values of the respective combinations in pairs, or from a variation calculation which tries to fulfill all three equations as well as possible. In the event D is already known, this can be utilized for further optimization.

After D and  $\Delta c_{bi}$  are ascertained, sodium distribution volume V is calculated in the arithmetic unit according to equation (8), where  $\Delta c_{bi} = c_{bi}(t + \Delta t) - c_{bi}(t)$  and  $\Delta t = t_1 - t_2$ .

For this purpose, arithmetic and evaluation unit 29 reads out the measured values for the dialyzing-fluid input and output concentrations  $c_{di}(t)$ ,  $c_{do}(t)$ , stored during the measurement in their chronological sequence, from memory unit 27. The measuring signals of the conductivity sensors are advantageously sampled, the calculation being carried out by a digital computer.

Assuming that the ascertained sodium distribution volume is essentially equal to the urea distribution volume, the urea distribution volume is determined and displayed on readout mechanism 30. From the known clearance K and treatment time t and the ascertained urea distribution volume V, arithmetic and evaluation unit 29 calculates the " $Kt/V$ " parameter which quantifies the dialyzing dosage. The " $Kt/V$ " parameter is likewise displayed on readout mechanism 30.

For the aforesaid reasons, the change in the dialyzing-fluid input concentration as a function of time should be symmetrical. However, if unsymmetrical pulses are used, it can no longer be assumed that  $c_{bi_0} = c_{bi_2}$ . Applicable in this case is:

$$cbi_2 = cbi_0 + \Delta cbi(I_1 + I_2)/I_1 \quad (14)$$

$$I_1 = \int_0^{t_1} [cdi(t) - cdo(t + td)] dt \quad (15)$$

$$I_2 = - \int_{t_1}^{t_2} [cdi(t) - cdo(t + td)] dt \quad (16)$$

Delay time  $td$  is the time after which the dialyzing-fluid output concentration rises after the increase of the dialyzing-fluid input concentration. Delay time  $td$  is calculated from the measured time profile of input and output concentrations  $cdi(t)$  and  $cdo(t)$ . It is evident from Figure 2 that, for the case of a symmetrical profile of  $cdi$ , integral surfaces  $I_1$  and  $I_2$  are nearly identical, which means, as assumed before,  $cbi_2 = cbi_0$ .

The sodium distribution volume is again calculated in arithmetic and evaluation unit 29 according to the equations (11) through (13), now, however,  $cbi_2 = cbi_0 + \Delta cbi(I_1 + I_2)/I_1$  being valid. The arithmetic and evaluation unit is provided with integrators for forming integrals  $I_1$  and  $I_2$ .

If ultrafiltration is carried on during the measurement, the sodium distribution volume can only be determined when the values  $cbi_{0,1,2}$  for the blood input concentration are known.

To this end, prior to measuring the distribution volume, the blood input concentration  $c_{bi}$  can be determined as described in detail in the German patent 39 38 662 C2, to which reference is specifically made. In this context, it is sufficient to ascertain an average value for  $c_{bi_{0,1,2}}$ .

Arithmetic and evaluation unit 29 now determines  $\Delta c_{bi}$  on the basis of the following equations:

$$D_{diff} = \frac{[(cdo_0 - cdi_0) - (cdo_1 - cdi_1)]Qd + [(c_{bi_1} - cdo_1) - (c_{bi_0} - cdo_0)]Qf}{\left(1 - \frac{Qf}{Qb}\right)[(c_{bi_0} - cdi_0) - (c_{bi_1} - cdi_1)]} \quad (17)$$

$$D_{diff} = \frac{[(cdo_1 - cdi_1) - (cdo_2 - cdi_2)]Qd + [(c_{bi_2} - cdo_2) - (c_{bi_1} - cdo_1)]Qf}{\left(1 - \frac{Qf}{Qb}\right)[(c_{bi_1} - cdi_1) - (c_{bi_2} - cdi_2)]} \quad (18)$$

$$D_{diff} = \frac{[(cdo_0 - cdi_0) - (cdo_2 - cdi_2)]Qd + [(c_{bi_2} - cdo_2) - (c_{bi_0} - cdo_0)]Qf}{\left(1 - \frac{Qf}{Qb}\right)[(c_{bi_0} - cdi_0) - (c_{bi_2} - cdi_2)]} \quad (19)$$

$D_{diff}$  represents the diffusive component of the dialysance.

The change as a function of time in the blood-input concentration  $\Delta c_{bi}$  is now determined in a similar manner as in the case of  $Q_f = 0$  from equations (17) through (19). The sodium distribution volume is then in turn calculated according to equation (8). Arithmetic and evaluation unit 29 thereupon again determines the urea distribution volume from the sodium distribution volume.

However, distribution volume  $V$  of a blood component in the body of an organism can also be determined in arithmetic and evaluation unit 29 without explicitly ascertaining the change as a function of time in the concentration of the component in the blood  $\Delta c_{bi}$ . To this end, device 17 again sets the profile, shown in Figure 2, for the dialyzing-fluid input concentration  $c_{di}(t)$ . The points of time "beginning", "end of the high phase" and "end of the low phase" are again indexed with 0, 1 and 2, respectively.

Dialysance  $D$  can be calculated as follows from the dialyzing-fluid input and output concentrations at points of time  $i, j$ :

$$D_{i,j} = \left( 1 - \frac{c_{do_i} - c_{do_j}}{c_{di_i} - c_{di_j}} \right) (Q_d + Q_f) \quad \text{time index } i \neq j \quad (20)$$

The above equation is derived assuming that the plasma-sodium is constant. However, this is not the case because of the salt transfer. If this assumption is not made, then the dialysance is calculated as follows:

$$D_{i,j} = \frac{\left[ (c_{do_i} - c_{di_i}) - (c_{do_j} - c_{di_j}) \right] Q_d + \left[ (c_{bi_j} - c_{do_j}) - (c_{bi_i} - c_{do_i}) \right] Q_f}{(c_{bi_i} - c_{di_i}) - (c_{bi_j} - c_{di_j})} + Q_f \quad (21)$$

Analogously, the diffusive component of dialysance  $D_{diff}$  for a constant plasma-sodium concentration reads as follows:

$$D_{diff\ i,j} = \frac{\left[ (c_{do_i} - c_{di_i}) - (c_{do_j} - c_{di_j}) \right] Q_d + (c_{do_i} - c_{do_j}) Q_f}{\left( 1 - \frac{Q_f}{Q_b} \right) [(c_{di_j} - c_{di_i})]} \quad (22)$$

If the assumption is dropped, the diffusive component of dialysance  $D_{diff}$  is calculated as follows:

$$D_{diff\ i,j} = \frac{\left[(cdo_i - cdi_i) - (cdo_j - cdi_j)\right]Qd + \left[(cbi_j - cdo_j) - (cbi_i - cdo_i)\right]Qf}{\left(1 - \frac{Qf}{Qb}\right)\left[(cbi_i - cdi_i) - (cbi_j - cdi_j)\right]} \quad (23)$$

Experiments have shown that, for the step-index profile shown in Figure 2, equations (20) and (22), respectively, are a good approximation for equations (21) and (23), respectively, for  $i=1$  and  $j=2$ .

If the values for the dialysance, which take into account the electrolyte transfer, are now compared to those resulting from a constant blood input concentration  $cbi$ , then distribution volume  $V$  can be determined.

To determine the distribution volume  $V$ , arithmetic and evaluation unit 29 first of all calculates, from the stored measured values, values  $D_{0,1}$ ,  $D_{1,2}$  and  $D_{diff1,2}$  according to equations (20) and (22) for dialysance  $D$  and the diffusive component of the dialysance  $D_{diff}$ . An ultra-filtration rate  $Qf$  of zero is preferably set when acquiring the measurable quantities  $cdi$  and  $cdo$ .

After determining the above values, the arithmetic and evaluation unit then calculates the distribution volume of the blood component according to the following equation:

$$V(t_1) = \left(\frac{D_{0,1}}{D_{1,2} - D_{0,1}} + 1\right) \cdot \left(\frac{D_{diff\ 1,2}(t_1 - t_0)(cdi_1 - cbi_0)}{cdi_1 - cdi_0}\right) \quad (24)$$



For a constant ultrafiltration rate, distribution volume V can be calculated for any points of time t as follows:

$$V(t) = V(t_1) + Q_f (t_1 - 1)$$

The concentration of the component in the blood  $c_{bi_0}$  (blood-input concentration) is determined beforehand according to equation (4a) or (4b). Namely, after the arithmetic and evaluation unit has determined the dialysance, the sought-after concentration  $c_{bi}$  is the single unknown.

The above equations show that it is not explicitly necessary to determine the change in the blood-input concentration as a function of time. It is sufficient to determine this variable at point of time  $t_0$ .

Equation (24) was derived assuming that the measurable quantities are recorded only a few minutes after a change in the dialyzing-fluid input concentration, and a shift of electrolytes through the dialyzer membrane proportional to the time ensues. It was further assumed that the recirculation in the fistula of the patient can be disregarded. To expand the validity range as a function of time and to take into account the recirculation, it is also possible to allow for empirically ascertained correction factors  $a_1$  for  $D_{0,1}$ ,  $D_{1,2}$  and  $D_{diff1,2}$  in equation (24). The calculation is then carried out according to the following equation:

$$V(t_1) = \left( \frac{a_1 D_{0,1}}{a_2 D_{1,2} - a_1 D_{0,1}} + 1 \right) \cdot \left( \frac{a_3 D_{diff1,2} (t_1 - t_0) (c_{di_1} - a_4 c_{bi_0})}{c_{di_1} - c_{di_0}} \right) \quad (25)$$



What is claimed is:

1. A method for determining the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment, in which the blood to be treated flows in an extracorporeal circuit through the blood chamber of a dialyzer subdivided by a semipermeable membrane into the blood chamber and a dialyzing-fluid chamber, and dialyzing fluid flows in a dialyzing-fluid path through the dialyzing-fluid chamber of the dialyzer, comprising the following method steps:

bringing about a change in the concentration of a blood component in the blood upstream of the dialyzer by a change in a physical or chemical characteristic in the dialyzing fluid upstream of the dialyzer; and

measuring the change in the physical or chemical characteristic in the dialyzing fluid downstream of the dialyzer which can be attributed to the change in the concentration of the blood component in the blood; and

determining the distribution volume  $V$  of the blood component from the change in the physical or chemical characteristic in the dialyzing fluid upstream and downstream of the dialyzer.

2. A method for determining the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment, in which the blood to be treated flows in an extracorporeal circuit through the blood chamber of a dialyzer subdivided by a semipermeable membrane into the blood chamber and a dialyzing-fluid

chamber, and dialyzing fluid flows in a dialyzing-fluid path through the dialyzing-fluid chamber of the dialyzer, comprising the following method steps:

- a physical or chemical characteristic of the dialyzing fluid is altered in the dialyzing-fluid path upstream of the dialyzer, and the physical or chemical characteristic of the dialyzing fluid is measured downstream of the dialyzer;

- the change as a function of time in the concentration of a blood component in the blood upstream of the dialyzer  $\Delta c_{bi}$  is determined from the physical or chemical characteristic of the dialyzing fluid upstream and downstream of the dialyzer; and

- the distribution volume  $V$  of the blood component is determined from the change as a function of time in the concentration of a blood component in the blood.

3. The method as recited in Claim 1 or 2, wherein the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path is measured upstream of the dialyzer.

4. The method as recited in one of Claims 1 through 3, wherein the physical or chemical characteristic of the dialyzing fluid upstream and downstream, respectively, of the dialyzer is the substance concentration in the dialyzing fluid upstream of the dialyzer (dialyzing-fluid input concentration  $c_{di}$ ) and downstream of the dialyzer (dialyzing-fluid output concentration  $c_{do}$ ).

5. The method as recited in Claim 4, wherein the conductivity of the dialyzing fluid is

measured as the physical or chemical characteristic for determining the distribution volume of sodium in the blood.

6. The method as recited in Claim 5, wherein the sodium distribution volume is ascertained for determining the distribution volume of urea in the blood, and the urea distribution volume is determined from the sodium distribution volume.

7. The method as recited in Claim 6, wherein the urea distribution volume is determined under the assumption that the sodium distribution volume essentially corresponds to the urea distribution volume.

8. The method as recited in one of Claims 1 through 7, wherein the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path is increased at a point of time  $t_0$  from a predetermined first value  $cdi_0$  to a predetermined second value  $cdi_1$ , is reduced at a point of time  $t_1 > t_0$  to a predetermined third value  $cdi_2$ , and is increased at a point of time  $t_2 > t_1$  to a predetermined fourth value  $cdi_0$  which is equal to the first value, the value by which the characteristic is increased being half as large as the value by which the characteristic is reduced.

9. The method as recited in Claim 8, wherein the time interval  $t_1 - t_0$  is equal to the time interval  $t_2 - t_1$ .

10. The method as recited in Claim 8 or 9, wherein the change as a function of time in the concentration of a blood component in the blood upstream of the dialyzer  $\Delta c_{bi}$  is ascertained from:

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the predetermined first value  $cdi_0$  of the physical or chemical characteristic of the dialyzing fluid upstream of the dialyzer and the value  $cdo_0$  of the characteristic that ensues downstream of the dialyzer, and the predetermined second value  $cdi_1$  of the characteristic upstream of the dialyzer and the value  $cdo_1$  of the characteristic which ensues downstream of the dialyzer after the increase in the characteristic upstream of the dialyzer to the predetermined second value, and the predetermined third value  $cdi_2$  of the characteristic upstream of the dialyzer and the value  $cdo_2$  of the characteristic which ensues downstream of the dialyzer after the decrease in the characteristic upstream of the dialyzer to the predetermined third value.

11. The method as recited in Claim 10, wherein the dialyzing fluid is balanced such that the volume of the dialyzing fluid flowing into the dialyzer during the measurement is equal to the volume of the dialyzing fluid flowing out of the dialyzer.

12. An apparatus for determining the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment in conjunction with an extracorporeal blood-treatment device, in which the blood to be treated flows in an extracorporeal circuit through the blood chamber (3) of a dialyzer (1) subdivided by a semipermeable membrane (2) into the blood chamber and a dialyzing-fluid chamber (4), and dialyzing fluid flows in a dialyzing-fluid path through the dialyzing-fluid chamber of the dialyzer, having

a device (17) for altering the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path upstream of the dialyzer, [and]

a measuring device (24) for determining the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path downstream of the dialyzer,

characterized by an arithmetic and evaluation unit (29) which is designed in such a way that the distribution volume V of the blood component can be determined from a change in the physical or chemical characteristic in the dialyzing fluid downstream of the dialyzer which can be attributed to the change in the concentration of a blood component in the blood because of a change in the physical or chemical characteristic in the dialyzing fluid upstream of the dialyzer.

13. An apparatus for determining the distribution volume of a blood component in the body of an organism during an extracorporeal blood treatment in conjunction with an extracorporeal blood-treatment device, in which the blood to be treated flows in an extracorporeal circuit through the blood chamber (3) of a dialyzer (1) subdivided by a semipermeable membrane (2) into the blood chamber and a dialyzing-fluid chamber (4), and dialyzing fluid flows in a dialyzing-fluid path through the dialyzing-fluid chamber of the dialyzer, having

a device (17) for altering the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path upstream of the dialyzer, [and]

a measuring device (24) for determining the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path downstream of the dialyzer,

characterized by an arithmetic and evaluation unit (29) which is designed in such a way that the change as a

function of time in the concentration of the blood component  $\Delta c_{bi}$  in the blood upstream of the dialyzer can be determined from the physical or chemical characteristic of the dialyzing fluid upstream and downstream of the dialyzer, and the distribution volume  $V$  of the blood component can be determined from the change as a function of time in the concentration of the blood component upstream of the dialyzer.

14. The apparatus as recited in Claim 12 or 13, wherein a measuring device (23) is provided for detecting the physical or chemical characteristic of the dialyzing fluid in the dialyzing-fluid path upstream of the dialyzer (1).

15. The apparatus as recited in one of Claims 12 through 14, wherein the device (17) for altering the physical or chemical characteristic is designed as a device for altering the substance concentration of the dialyzing fluid upstream of the dialyzer (dialyzing-fluid input concentration  $c_{di}$ ).

16. The apparatus as recited in one of Claims 12 through 15, wherein the measuring devices (23,24) for detecting the physical or chemical characteristic are designed as measuring devices for detecting the substance concentration of the dialyzing fluid downstream and upstream, respectively, of the dialyzer (dialyzing-fluid output concentration  $c_{do}$  and input concentration  $c_{di}$ ).

17. The apparatus as recited in Claim 16, wherein the first and second measuring devices (23,24) for detecting the physical or chemical characteristic



have a conductivity sensor, optical sensor or enzyme sensor arranged in the dialyzing-fluid path downstream and upstream, respectively, of the dialyzer.

18. The apparatus as recited in one of Claims 12 through 17,

wherein the device (17) for altering the physical or chemical characteristic is designed in such a way that the characteristic is increased at a point of time  $t_0$  from a predetermined first value  $cdi_0$  to a predetermined second value  $cdi_1$ , is reduced at a point of time  $t_1 > t_0$  to a predetermined third value  $cdi_2$ , and is increased at a point of time  $t_2 > t_1$  to a predetermined fourth value  $cdi_0$  which is equal to the first value, the value by which the characteristic is increased being half as large as the value by which the characteristic is reduced.

19. The apparatus as recited in Claim 18, wherein the time interval  $t_1 - t_0$  is equal to the time interval  $t_2 - t_1$ .

20. The apparatus as recited in Claim 18 or 19, wherein the arithmetic and evaluation unit (29) is designed in such a way that the predetermined first, second and third values  $cdi_0$ ,  $cdi_1$ ,  $cdi_2$  of the physical or chemical characteristic of the dialyzing fluid upstream of the dialyzer (1) and the values  $cdo_0$ ,  $cdo_1$ ,  $cdo_2$  of the physical or chemical characteristic of the dialyzing fluid ensuing downstream of the dialyzer are evaluable for determining the change as a function of time in the concentration of the blood component  $\Delta cbi$ .

21. The apparatus as recited in one of Claims 12 through 20,

wherein a balancing device (10) is provided with which

the dialyzing fluid can be balanced in such a way that the volume of the dialyzing fluid flowing into the dialyzer (1) during the measurement is equal to the volume of the dialyzing fluid flowing out of the dialyzer.

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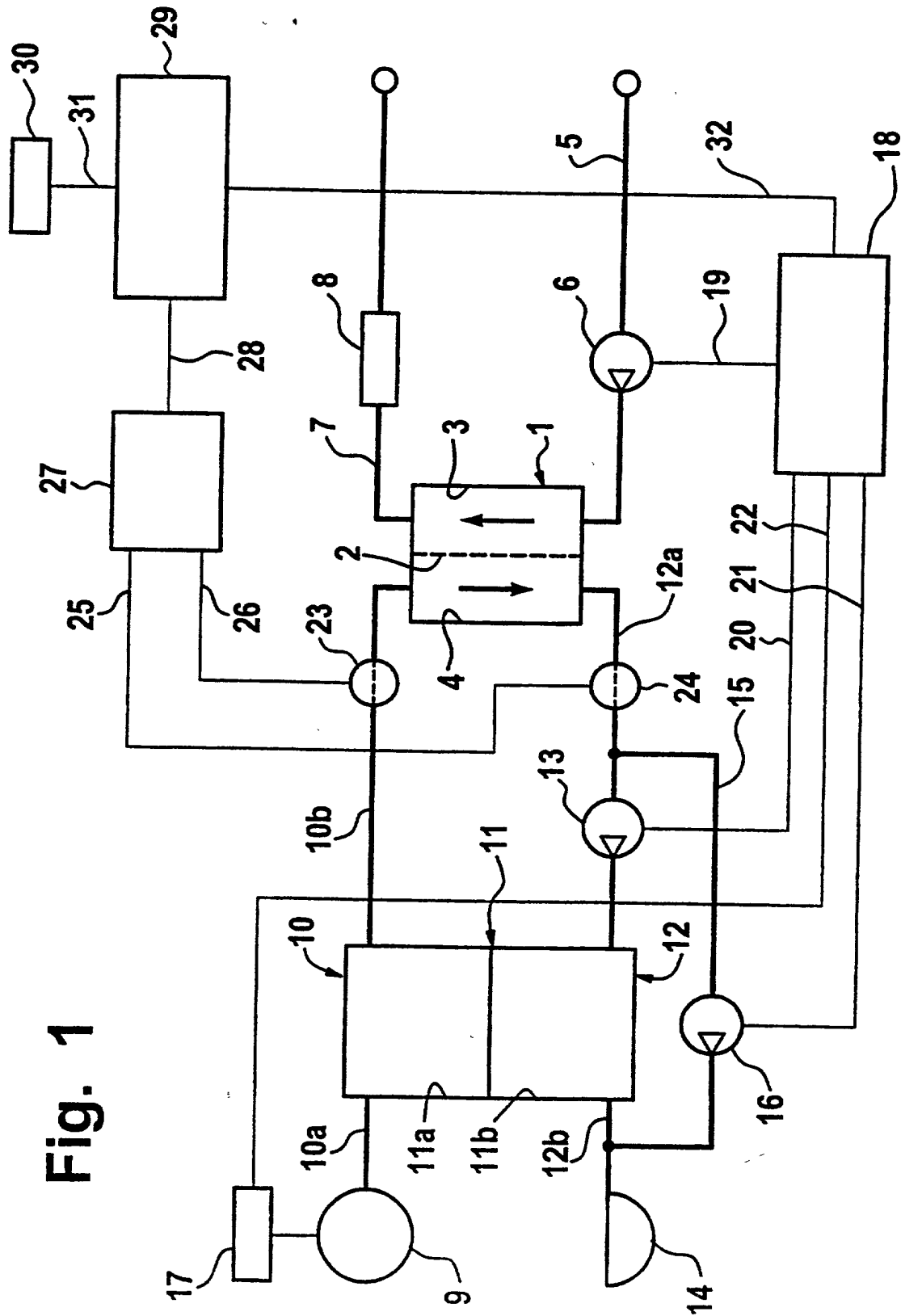
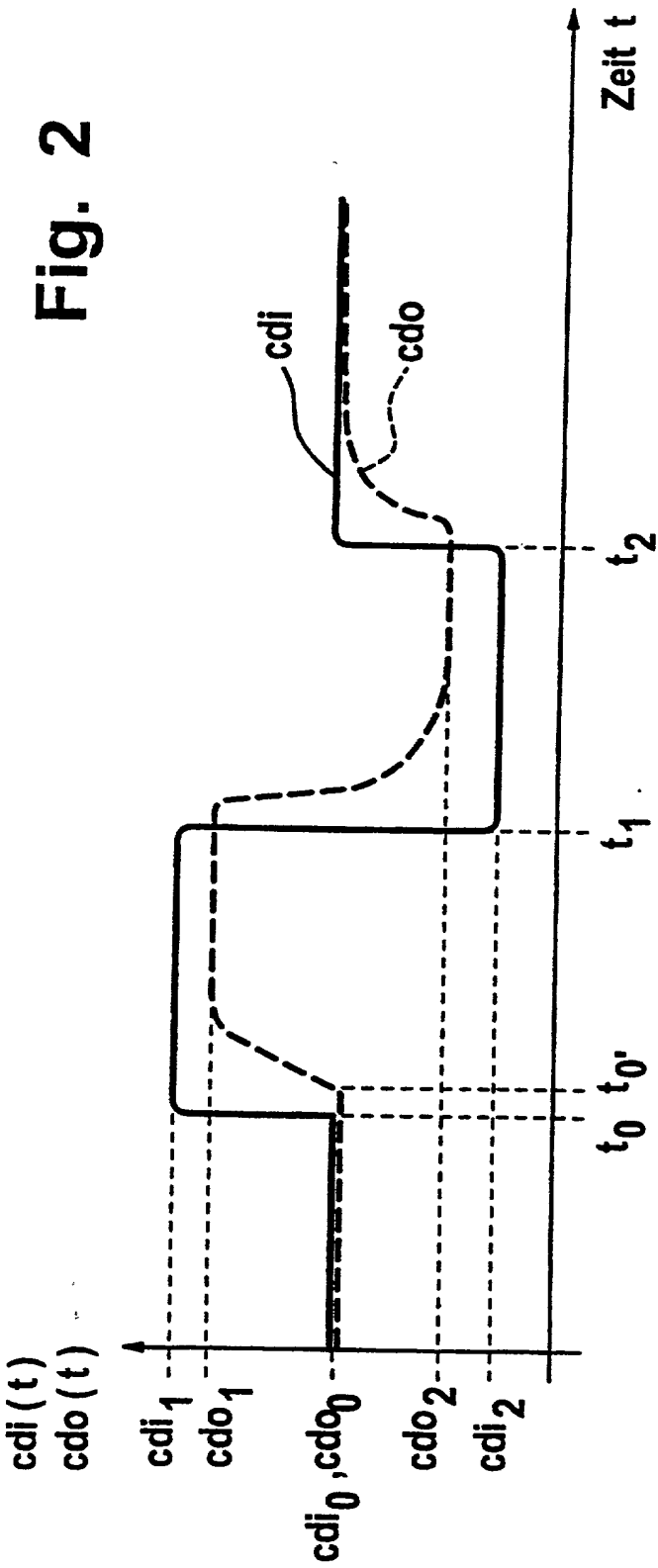


Fig. 1



93/24/112  
#3



Docket No.: 2565/86

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original and first and joint inventor of the subject matter that is claimed and for which a patent is sought on the invention entitled **METHOD FOR DETERMINING THE DISTRIBUTION VOLUME OF A BLOOD COMPONENT DURING AN EXTRACORPOREAL BLOOD TREATMENT AND APPARATUS FOR IMPLEMENTING THE METHOD**, the specification of which was filed in the United States Patent and Trademark Office on June 22, 2001, Serial No. 09/868,950.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge the duty to disclose information that is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

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PRIOR FOREIGN APPLICATION(S)

<u>198 60 330.4</u>	<u>Germany</u>	<u>24 December 1998</u>	Yes <u>X</u> No <u>    </u>
(Number)	(Country)	(Day/month/year filed)	Priority Claimed Under 35 USC 119

And I hereby appoint Thomas J. Meloro (Registration No. 33,538), Jeffrey S. Ginsberg (Registration No. 36,148), and David I. Greenbaum (Registration No. 46,739) my attorney with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Please address all communications regarding this application to:



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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



#3  
12/14/01  
Docket No.: 2565/86

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#3  
98/37 100  
Docket No.: 2565/86

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DURING AN EXTRACORPOREAL BLOOD TREATMENT AND APPARATUS FOR  
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1-00

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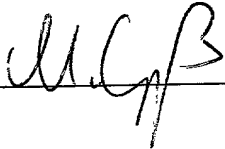
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3-00

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09868950 110501